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Influence of Ranitidine, Pirenzepine, and Aluminum Magnesium Hydroxide on the Bioavailability of Various Antibiotics, Including Amoxicillin, Cephalexin, Doxycycline, and Amoxicillin-Clavulanic Acid

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Two randomized double-blind crossover studies and one randomized crossover study were performed to document possible drug-drug interactions between antacids (aluminum magnesium hydroxide, 10 ml per dose for 10 doses), antimuscarinic drugs (pirenzepine, 50 mg per dose for 4 doses), and H_2-blockers (ranitidine, 150 mg per dose for 3 doses) and amoxicillin (1,000 mg), cephalexin (1,000 mg), doxycycline (200 mg), and amoxicillin-clavulanic acid (625 mg). Ten healthy volunteers participated in each study. Concentrations in serum and urine were measured by bioassay, and pharmacokinetic parameters were calculated by the usual open one- or two-compartment models (statistics were determined by the Wilcoxon test). The antacid, pirenzepine, and ranitidine had no influence on the bioavailability of amoxicillin, cephalexin, and amoxicillin-clavulanic acid. Only small differences could be observed in the pharmacokinetic parameters, but they are not of therapeutic importance. However, the antacid caused a significant ($P < 0.01$) reduction in the gastrointestinal absorption of doxycycline (area under the concentration-time curve, 38.6 ± 22.7 mg · h/liter, fasting; 6.0 ± 3.2 mg · h/liter, with antacid), resulting in subtherapeutic levels of doxycycline.

There is an increasing number of polymorbid and geriatric patients who must be treated simultaneously with different pharmacological substances. Thus, interactions of different drugs are an increasing problem in current therapy. Recently, studies revealed that the bioavailability of the new 4-fluoroquinolones was reduced by antacids (14, 31). Amoxicillin, cephalexin, doxycycline, and amoxicillin-clavulanic acid are frequently used antibiotic agents with a wide antibacterial spectrum, e.g., against urinary and respiratory pathogens (26, 36, 50). Each of these substances exhibits a different pattern of pharmacokinetic behavior after oral administration. They are chiefly administered orally to elderly patients in the outpatient department.

Drug interactions may occur at the site of absorption, and prediction of possible interactions is important because of toxicity and efficacy. Modification in the gastrointestinal tract such as changes in pH or changes of gastrointestinal motility is the reason for accelerated, increased, or reduced bioavailability (10, 18). The prediction of such interactions is of clinical interest for therapy.

MATERIALS AND METHODS

Study design. The investigation consisted of three different studies. Two studies were performed to investigate the influence of pirenzepine (antimuscarinic drug) and ranitidine (H_2-blocker) on the bioavailability of amoxicillin, cephalexin, and doxycycline. In the first study, the volunteers received either ranitidine tablets or placebo tablets, and in the second study, they received either pirenzepine tablets or placebo tablets as a concomitant drug to the antibiotics. Both studies were designed as randomized double-blind crossover studies. In the third study, we determined the influence of an antacid [$Al(OH)_3$-$Mg(OH)_2$] on the bioavailability of amoxicillin, cephalexin, doxycycline, and amoxicillin-clavulanic acid. This study was a randomized crossover study.

Volunteers. In each of the three studies, 10 healthy volunteers participated, five women and five men. They had mean body weights of 66.8 ± 6.8 kg (study 1, ranitidine), 64.2 ± 5.4 kg (study 2, pirenzepine), or 66 ± 8 kg (study 3, antacid) and mean ages of 29.6 ± 6.5 years (study 1), 31.7 ± 7.3 years (study 2), or 27 ± 4 years (study 3). Subjects had normal kidney and liver function as well as normal biochemical and hematological laboratory profiles; no drug intake or oral contraceptives were allowed during the 4-week period before the studies and during the studies themselves.

Concomitant drugs. Pirenzepine (50 mg per tablet, Ch.-B: 12.118-0; Thomae GmbH, Biberach an der Riss, Federal Republic of Germany) or placebo was given at a total dosage of 200 mg: three tablets on the day before and one tablet with each antibiotic. The volunteers were treated with 450 mg of ranitidine or placebo (Ch.-B 74459). Two tablets (one tablet = 150 mg of ranitidine; Ch.-B 7435; Cascan GmbH, Wiesbaden, Federal Republic of Germany) were given on the day before and one tablet was given on the experimental day together with the antibiotic. The antacid Maalox 70 [10 ml = 900 mg of $Al(OH)_3$ plus 600 mg of $Mg(OH)_2$; gel; Ch. 536947; Müller-Rorer, Bielefeld, Federal Republic of Germany] was given in at a total dosage of 100 ml, 10 ml per dose for eight doses on the day before and 10 ml per dose for two doses on the experimental day. The last dose was administered 30 min before intake of the antibiotics.

Antibacterial agents. Amoxicillin (1,000 mg; tablets; Ch. 83 EW 17/6178; Beecham-Wülfing, Neuss, Federal Republic of Germany), cephalexin (1,000 mg; tablets; Ch. 02558 E B A; Thomae GmbH), doxycycline (200 mg; tablets; Ch. 520630; Pfizer, Karlsruhe, Federal Republic of Germany), and amoxicillin-clavulanic acid (625 mg [500 mg of amoxicillin plus 125

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mg of clavulanic acid]; Augmentin; tablets; Ch. 85 F 20/1090; Beecham-Wülfing).

Subjects fasted for 10 h before antibiotic administration. The oral drugs were swallowed with 100 ml of tap water. The first water intake was allowed 1 h and the first food intake was allowed 2 h after administration of the test substances (without caffeine-containing beverages).

To verify the compliance of the volunteers and to document therapeutic levels of the H_2-blocker and the antimuscarinic drug, we collected serum samples for measuring pirenzepine and ranitidine during the investigation. Concentrations of ranitidine and pirenzepine in serum were measured by different techniques. Ranitidine was determined by high-performance liquid chromatography (4). To determine pirenzepine, we used a radioimmunoassay (45).

Sampling. Blood samples were obtained from the cubital vein just before administration and 10, 20, 30, 60, 90, 120, 180, 240, 360, 480, 600, 720, and 1,440 min after intake of the antibacterial agents. Urine was collected at intervals of 0 to 3 h, 3 to 6 h, 6 to 12 h, and 12 to 24 h. All serum samples were immediately separated and stored at −70°C until assayed together with the urine samples.

Microbiological assay. We used the agar diffusion test modified by Reeves and Bywater (35) for measurement of concentrations in serum and urine. The assay was performed with nutrient agar (1.5% agar medium 2; Oxoid Ltd., London, England). Pooled normal human serum (pH fixed at 7.4) was used as a diluent for serum specimens; 0.5 M Sörensen phosphate buffer (pH 7.0) was used for urine samples and standards. Test substances for the standard solutions were amoxicillin trihydrate (Ch. CRL 2333), cephalexin monohydrate (Ch. C3 × 2301), doxycycline monohydrate, and potassium clavulanate (100 mg of free acid; Ch. BRL 14151). Test species were *Sarcinia lutea* NCTC 8340 for low concentrations of cephalexin and amoxicillin (<0.3 mg/liter) and *Bacillus subtilis* ATCC 6633 for high concentrations of both substances. Amoxicillin in amoxicillin-clavulanic acid was tested with *S. lutea* NCTC 8340. The concentrations of clavulanic acid in serum were determined by using its ability to inhibit certain bacterial β-lactamases in a microbiological assay. Benzylpenicillin (5 mg/liter) was added to nutrient agar inoculated with the β-lactamase-producing *Klebsiella aerogenes* NCTC 11228. Clavulanic acid does not inhibit the growth of *K. aerogenes* but does inhibit β-lactamase production, thus preventing destruction of the benzylpenicillin. The inhibition zones produced by benzylpenicillin are proportional to the logarithmic concentrations of clavulanic acid in the test samples.

The lowest detectable activities in serum were as follows: amoxicillin, 0.015 mg/liter; cephalexin, 0.3 mg/liter; doxycycline, 0.06 mg/liter; and clavulanic acid, 0.06 mg/liter. Precision of the agar diffusion test from day to day for all administered antibiotics ranged from 1.1 to 7.1% (coefficient of variation) for concentrations of 0.1 to 20 mg/ml.

Pharmacokinetic calculations. Pharmacokinetic parameters of amoxicillin, cephalexin, doxycycline, and clavulanic acid were calculated by using the usual open one- or two-compartment models (11, 37, 40). An iterative least-squares method was used to fit the regression curve to the experimentally obtained values of the serum concentration-time curve after normalization of the concentrations in serum to a mean body weight of 70.0 kg (19, 33). Mathematical calculation of the constants and pharmacokinetic parameters was performed by standard methods as previously described (11, 22). The following pharmacokinetic parameters were calculated: peak level in serum (C_{max}), time taken to reach the peak level (T_{max}), area under the curve (AUC, extrapolated to infinity), biological half-life ($t_{1/2\beta}$) in the elimination phase, and the volume of distribution (V_{area}).

Statistical evaluation. The important pharmacokinetic parameters of bioavailability—C_{max}, T_{max}, and AUC—were used to compare the single dose with the combined administration. The Wilcoxon test for paired differences was used to distinguish these parameters. A P value of <0.05 was considered significant; a P value of <0.01 was highly significant.

RESULTS

During the studies, we obtained therapeutic levels of both ranitidine and pirenzepine. The mean concentration in serum of ranitidine was 89.8 ± 67.9 ng/ml (12 h after the last dose), and those of pirenzepine were 83.3 ± 34.4 ng/ml 1 h after the last dose and 49.6 ± 14.3 ng/ml 6 h after intake of the last dose.

Amoxicillin. Pirenzepine had no effect on the concentrations of amoxicillin in serum. The other pharmacokinetic parameters, such as AUC, T_{max}, and urinary recovery, were likewise unaffected (Table 1). Simultaneous administration of amoxicillin and ranitidine led to slightly decreased maximum concentrations of amoxicillin in serum. Because of the lack of alteration in the basic pharmacokinetic parameters including V_{area}, we assume that the bioavailability did not change (Table 1).

Mean concentrations in serum of amoxicillin alone and amoxicillin in combination with the antacid are depicted in Fig. 1.

The antacid led to a significant decrease of T_{max} and increase of C_{max} ($P < 0.01$). AUC, however, representing one important factor of bioavailability, did not change (Table 1). The other parameters listed in Table 1 were unchanged as well.

Cephalexin. Almost none of the pharmacokinetic parameters of cephalexin were affected by any of the coadministered drugs (Table 2). Ranitidine, pirenzepine, or the antacid did not alter the extent of absorption. Although the mean maximum concentrations of cephalexin in serum decreased from 29.2 ± 7.0 mg/liter (placebo) to 24.1 ± 5.1 mg/liter with ranitidine ($P < 0.05$), the AUC did not alter. After cephalexin was given together with the antacid, urinary recovery (24 h) was significantly decreased (74.2 ± 16.6% of dose, $P < 0.01$), while AUC, T_{max}, and C_{max} demonstrated no differences (Table 2).

Doxycycline. Pirenzepine did not influence the gastrointestinal absorption of doxycycline, as indicated by C_{max} and AUC in Table 2. Pirenzepine prolonged the absorption time (T_{max}) of doxycycline from 126 ± 49 min (placebo) to 204 ± 41 min ($P < 0.01$). $t_{1/2\beta}$ was slightly accelerated by pirezenpine. In the control group, it lasted 929 ± 180 min versus 539 ± 108 min in the pirenzepine group. Ranitidine plus doxycycline showed characteristics similar to those of pirenzepine plus doxycycline. The main parameters of bioavailability remained unchanged if doxycycline was administered with either placebo or ranitidine. We observed only an increased elimination half-life of doxycycline. For doxycycline with ranitidine, the $t_{1/2\beta}$ of doxycycline was 918 ± 326 min, whereas for doxycycline with placebo, $t_{1/2\beta}$ was 639 ± 132 min ($P < 0.01$). Administration of doxycycline after pretreatment with the antacid resulted in a significant reduction of gastrointestinal absorption. The antacid reduced the availability of doxycycline by nearly 85%. The relative

TABLE 1. Influence of pirenzepine, ranitidine, and antacid (Maalox 70) on bioavailability of amoxicillin and clavulanic acid[a]

Antibiotic agent[b] (mg)	Coadministered drug[c]	C_{max} (mg/liter)	T_{max} (min)	$t_{1/2\beta}$ (min)	V_{area} (liters)	AUC_{total} (mg · h/liter)	Urinary recovery (% of dose)
Amoxicillin (1,000)	Placebo	13.5 (2.6)	70.1 (16.0)	72.5 (8.3)	47.6 (5.8)[d]	37.2 (6.0)	53.0 (7.9)
	Pirenzepine	12.5 (2.9)	75.8 (8.3)	77.7 (7.8)	50.3 (10.3)[d]	38.4 (8.0)	49.4 (10.3)
	Placebo	11.4 (3.5)	93.9 (31.4)	72.3 (7.7)	43.9 (14.6)[e]	38.4 (9.0)	49.1 (7.3)
	Ranitidine	10.0 (3.3)*	96.9 (13.7)	73.4 (9.5)	54.3 (10.2)[e]	33.3 (6.1)	49.8 (13.0)
	Fasting	12.4 (5.3)	116.2 (20.3)	107.7 (23.8)	283 (135)[d]	35.5 (14.8)	51.3 (12.8)
	Antacid	15.0 (5.7)**	87.1 (15.2)**	165.8 (54.4)	240 (82)[e]	34.3 (13.4)	48.3 (14.9)
AUG (amoxicillin, 500)	Fasting	8.3 (3.7)	122.1 (31.0)	107.8 (24.5)	223 (103)[e]	21.9 (8.6)	64.7 (15.9)
	Antacid	9.0 (3.6)	101.6 (23.0)**	85.3 (17.1)	230 (149)[d]	18.9 (5.8)	65.2 (14.8)
AUG (clavulanic acid, 125)	Fasting	3.4 (1.4)	97.8 (44.4)	72.9 (9.1)	60.9 (29.1)[d]	6.9 (2.3)	41.0 (21.6)
	Antacid	3.4 (1.3)	83.5 (23.6)	77.9 (8.7)	61.4 (20)[d]	6.5 (1.4)	34.2 (14.5)

[a] Pharmacokinetic parameters are expressed as mean (standard deviation) in 10 healthy volunteers. *, $P < 0.05$; **, $P < 0.01$.
[b] AUG, Amoxicillin-clavulanic acid.
[c] Antacid, Aluminum magnesium hydroxide (Maalox 70).
[d] One-compartment model.
[e] Two-compartment model.

bioavailability was 15.5% when doxycycline was taken with the antacid. Figure 2 demonstrates the mean concentrations in serum of doxycycline alone and after pretreatment with the antacid. The AUC was reduced from 38.6 ± 22.7 mg · h/liter with doxycycline alone to 6.0 ± 3.2 mg · h/liter with doxycycline in combination with the antacid ($P < 0.01$). Maximum concentrations of doxycycline in serum were also reduced from 2.7 ± 1.7 mg/liter without antacid to 0.5 ± 0.2 mg/liter with the antacid ($P < 0.01$). Urinary recovery (Fig. 3) of doxycycline was only 4.9% when the dose was coadministered with the antacid versus 17.7% when the dose was administered alone ($P < 0.01$).

Amoxicillin-clavulanic acid. Amoxicillin in amoxicillin-clavulanic acid demonstrated characteristics similar to those of amoxicillin as a single drug (Table 1). The antacid also accelerated gastrointestinal absorption of amoxicillin in amoxicillin-clavulanic acid. After an oral dose of amoxicillin-clavulanic acid, maximum concentrations of amoxicillin in serum in the fasting state were observed at 122 ± 31 min for the drug administered alone and at 101 ± 23 min for the drug with antacid ($P < 0.01$).

Peak concentrations in serum demonstrated a tendency toward higher levels similar to the effect on amoxicillin as a single dose, but there was no effect on any of the other pharmacokinetic parameters. Therefore, we assume that bioavailability was unaffected (Table 1).

The antacid did not change the pharmacokinetics of clavulanic acid in amoxicillin-clavulanic acid. Therefore, bio-

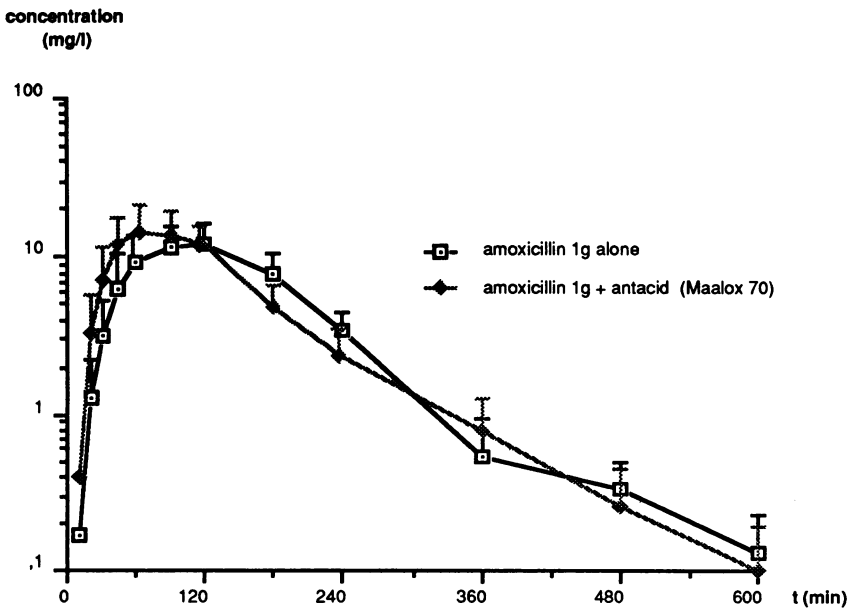

FIG. 1. Mean (+ standard deviation) concentrations in serum of amoxicillin alone and amoxicillin plus antacid in 10 healthy volunteers.

TABLE 2. Influence of pirenzepine, ranitidine, and antacid (Maalox 70) on bioavailability of cephalexin and doxycycline[a]

Antibiotic agent (mg)	Coadministered drug[b]	C_{max} (mg/liter)	T_{max} (min)	$t_{1/2\beta}$ (min)	V_{area} (liters)	AUC (mg · h/liter)	Urinary recovery (% of dose)
Cephalexin (1,000)	Placebo	24.9 (12.1)	52.2 (24.2)	54.3 (9.6)	23.1 (4.2)[c]	57.2 (8.8)	95.4 (15.8)
	Pirenzepine	26.5 (7.7)	69.3 (27.8)	49.5 (8.5)	19.8 (3.7)[c]	60.2 (8.0)	95.9 (8.6)
	Placebo	29.9 (7.0)	55.6 (19.6)	84.3 (39.5)	34.9 (16.9)[d]	58.8 (9.6)	83.4 (14.9)
	Ranitidine	24.1 (5.1)*	69.7 (18.4)	135.0 (115)	58.5 (54.0)[d]	58.0 (7.6)	83.7 (17.3)
	Fasting	29.8 (10.2)	85.1 (19.8)	60.6 (12.4)	42.9 (13.6)[c]	56.1 (14.0)	90.2 (9.7)
	Antacid	29.9 (6.9)	72.5 (30.1)	89.1 (13.1)	44.5 (8.1)[d]	57.0 (11.3)	74.2 (16.6)*
Doxycycline (200)	Placebo	3.1 (1.4)	126 (49.0)	929 (18)	79.1 (20.9)[d]	59.5 (16.8)	22.6 (4.6)
	Pirenzepine	2.9 (0.6)	204 (41.2)	592 (108)**	56.3 (16.7)[d]	53.0 (12.6)	21.7 (4.7)
	Placebo	2.8 (1.0)	171 (65.8)	639 (132)	93.0 (32.0)[d]	49.5 (22.8)	20.9 (6.0)
	Ranitidine	2.7 (1.1)	162 (32.2)	918 (326)**	111.0 (53.4)[d]	48.2 (21.6)	21.4 (8.9)
	Fasting	2.7 (1.6)	114.2 (61.7)	835 (230)	191.5 (63.4)[d]	38.6 (22.7)	17.7 (10.9)
	Antacid	0.45 (0.2)**	111.1 (35.8)	664 (197)	615.3 (228)**[d]	6.0 (3.2)**	4.0 (1.9)**

[a] Pharmacokinetic parameters are expressed as mean (standard deviation) in 10 healthy volunteers. *, $P < 0.05$; **, $P < 0.01$.
[b] Antacid, Aluminum magnesium hydroxide (Maalox 70).
[c] One-compartment model.
[d] Two-compartment model.

availability was unaltered by coadministration with the antacid. The results are summarized in Table 1.

DISCUSSION

All three simultaneously administered drugs, pirenzepine, ranitidine, and the antacid, have activity in the gastrointestinal tract. Antimuscarinic drugs like pirenzepine and propantheline have anticholinergic activity and reduce gastrointestinal motility and stomach-emptying rate (3, 5, 9, 30, 43).

H_2-receptor antagonists reduce H^+ activity in the stomach and thereby increase the pH of gastric fluid (48). In this way, they may alter the rate of gastric emptying and hence the rate of drug absorption. Drug-drug interactions between ranitidine and midazolam (6), β-blockers (42), or cobalamin (20) were reported.

Interactions involving coadministration of drugs with various antacid preparations are well documented (23, 51). Several mechanisms of action exist: raising the pH in the gastrointestinal tract, increasing solubility of acids and decreasing solubility of bases, adsorption to insoluble antacid particles, chelation to insoluble complexes, influencing the stomach-emptying rate and gastric acidity (15, 18, 46). The effect of the second drug may be a reduced, delayed, increased, or accelerated intestinal absorption.

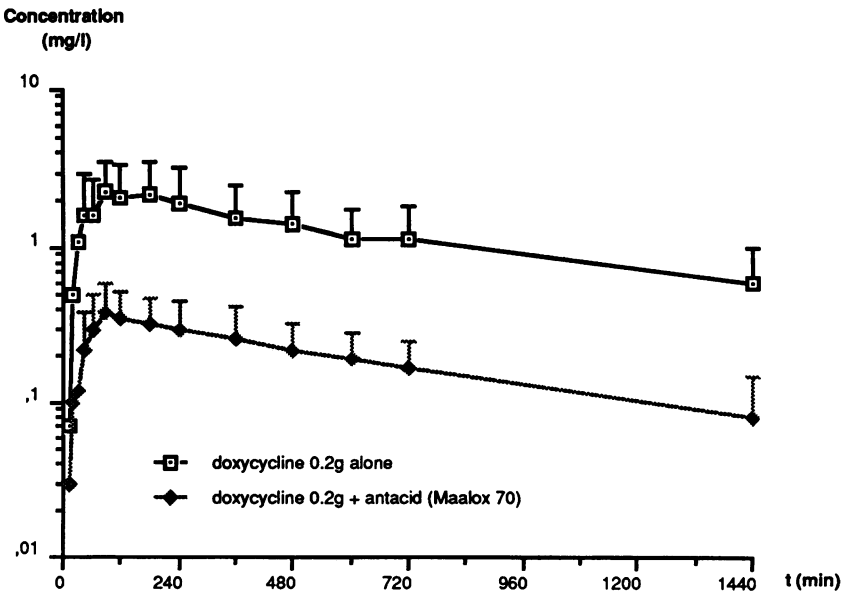

FIG. 2. Mean (+ standard deviation) concentrations in serum of doxycycline alone and doxycycline plus antacid in 10 healthy volunteers.

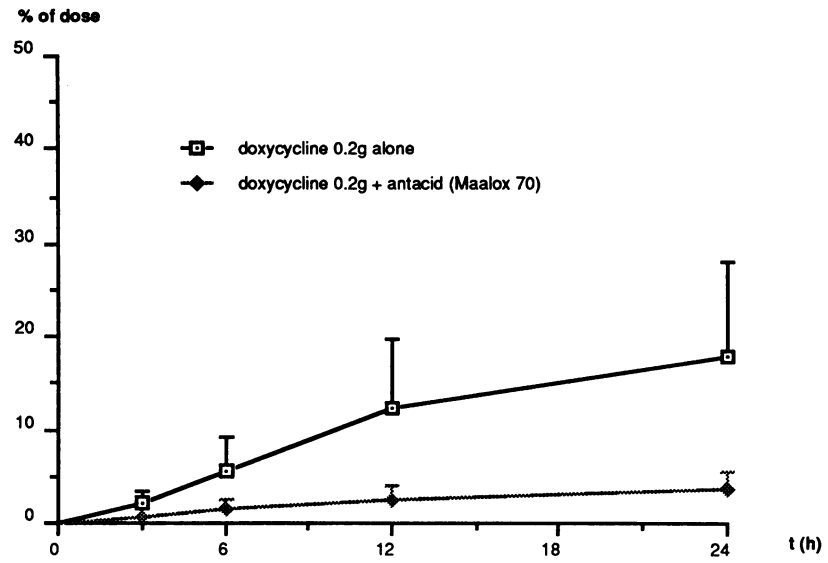

FIG. 3. Cumulative urinary recovery (+ standard deviation) of doxycycline alone and doxycycline plus antacid.

Amoxicillin. Administration of amoxicillin after a standard breakfast led to a delay in absorption and elevated maximum concentrations in serum but did not reduce bioavailability (26). Prednisolone likewise had no influence on the kinetics of amoxicillin (15). Few data are available on drug interactions with amoxicillin. Results obtained with the three substances coadministered with amoxicillin differed. While pirenzepine did not alter the pharmacokinetics of amoxicillin, ranitidine decreased mean levels of the antibiotic in serum from 11.4 ± 3.5 to 10 ± 2.3 mg/liter ($P < 0.05$). The observed effect was only a slight one and without therapeutic consequences. These data, however, are in contrast to those reported by Staniforth et al. (44). They administered cimetidine together with amoxicillin-potassium clavulanate and found significantly enhanced bioavailability of amoxicillin corresponding to higher peak levels and an elevated AUC. Cimetidine has been shown to inhibit hepatic microsomes (13). The effect of ranitidine on hepatic microsomes is controversial (8, 17, 41), and if there is an effect, it is only minor. To clarify the mechanism of the cimetidine-amoxicillin interaction, Staniforth et al. (44) did an additional study with cimetidine and parenterally administered amoxicillin-clavulanic acid. Here cimetidine had no effect. Staniforth et al. (44) therefore postulated that this effect is probably due to improved solubility of amoxicillin at a higher pH. Since amoxicillin has the lowest solubility at a pH range of 4 to 6, this mechanism is not very evident (47). Surprisingly, our studies revealed an accelerated absorption and elevated maximum concentrations of amoxicillin in serum when intake followed pretreatment with antacid. One explanation for the accelerated absorption may be an increased intestinal motility resulting from the osmotic effects of $Mg(OH)_2$ (24). Here our results are in good agreement with the results of Staniforth et al. (44), even demonstrating an increased C_{max} in connection with unaltered bioavailability of amoxicillin in combination with the antacid.

Cephalexin. Cephalexin is a well-investigated antibacterial agent. Lode (21) demonstrated that cephalexin is absorbed in the small intestine. Different formulations of cephalexin produce different concentrations in serum. Griffith and Black (12) found levels of cephalexin in serum to be twice as high in the monohydrate form as in the anhydrate form. Cholestyramine, an anionic-exchange resin, reduces bioavailability of cephalexin (32). No influence on gastrointestinal absorption was exerted by *N*-butylscopolamine, an anticholinergic drug (21).

In our investigations, we did not find any clinically relevant interactions between cephalexin and pirenzepine, ranitidine, or the antacid. Maximum concentrations of cephalexin in serum were reduced to 24 mg/liter when it was administered together with ranitidine. This seems to be in a normal range compared with the results obtained from others administering the same dose of cephalexin in the fasting state (25, 34). In vitro studies of Griffith and Black (12) demonstrated that the aqueous solubility of cephalexin is a function of pH. Solubility increases at either a low or high pH. At pH levels between 3 and 8, only a small amount of cephalexin is dissolved. Since cephalexin is absorbed from the small intestine (21), which has a pH range of 6 to 8, no influence is exerted by changes in H^+ activity of the gastric fluid.

After cephalexin administration in combination with the antacid, only 74.3% of the dose could be collected in the 24-h urine sample. A similar effect was described by Meyers et al. (24), who administered cephalexin after a standard meal.

Amoxicillin in amoxicillin-clavulanic acid. The administration of amoxicillin in combination with clavulanic acid does not influence the absorption of either drug (52). Furthermore, the bioavailability was not affected by food (16). Staniforth et al. (44) demonstrated that the concomitant intake of milk could reduce concentrations of amoxicillin in serum but not significantly.

Our data with coadministration of an antacid containing aluminum hydroxide and magnesium hydroxide with amoxicillin showed little change compared with the administration of the antibiotic alone. Maximum concentrations in serum were slightly increased, and absorption was significantly accelerated. Increased intestinal motility may be responsible for the accelerated absorption (24). No difference was observed in the bioavailability. These data are comparable to those reported by Staniforth et al. (44) administering aluminum hydroxide together with amoxicillin-clavulanic acid.

Clavulanic acid in amoxicillin-clavulanic acid. In accordance with the results of Staniforth et al. (44), clavulanic

acid in amoxicillin-clavulanic acid was unaffected by coadministered antacid in our investigations.

Doxycycline. The absorption of tetracyclines can be affected by many other drugs used concomitantly. One of the main mechanisms involves the ability of tetracyclines to form chelates with metal ions in a six-membered ring structure. In this way, Fe^{2+}, Al^{3+}, Ca^{2+}, Zn^{2+}, and Mn^{2+} are active substances (1, 49) and their coadministration with tetracycline derivatives leads to a significant decrease in concentrations in serum and bioavailability of the antibiotic. An influence on the gastrointestinal absorption of tetracyclines analogous to that of the metal ions is exerted by milk and sodium bicarbonate (2, 38, 39). Our investigations demonstrated a marked 85% reduction in doxycycline bioavailability compared with that in the fasting condition. AUC was decreased from 38.6 to 6 mg · h/liter after intake of the antacid. Maximum concentrations of doxycycline in serum were only 0.5 mg/liter when it was administered with the antacid. Therefore, bacteriostatic concentrations in serum could not be maintained. Rosenblatt et al. (38) reported similar results on the ingestion of aluminum hydroxide gel with either doxycycline or demeclocycline. Besides chelation, other mechanisms, for example, adsorption of doxycycline to antacid particles or altered gastrointestinal motility or pH, may also be involved.

With pirenzepine, ranitidine, and placebo, we observed different times for the elimination half-life of doxycycline. In previous oral studies (7), the mean $t_{1/2\beta}$ of doxycycline varied between 15 and 21 h. Moreover, the $t_{1/2\beta}$ of doxycycline showed a marked intersubject and intrasubject variability. The $t_{1/2\beta}$ of doxycycline was shortened from 929 ± 180 min with placebo to 539 ± 108 min ($P < 0.01$) when doxycycline was administered with pirenzepine. Previous studies reported an acceleration of elimination when doxycycline was given to patients receiving long-term therapy with barbiturates or anticonvulsants or after long-term alcohol consumption (27–29). In our investigation, volunteers received only a 1-day treatment with pirenzepine. There is no evidence that the observed effect on the half-life of doxycycline is due to the antimuscarinic drug.

In conclusion, pirenzepine, ranitidine, and the antacid do not affect the bioavailability of amoxicillin, cephalexin, and amoxicillin-clavulanic acid when administered simultaneously. Small differences in some pharmacokinetic parameters were observed, but they are unlikely to be of therapeutic relevance. Therefore, these substances can be administered together.

Doxycycline bioavailability was not reduced by pirenzepine and ranitidine but was significantly altered by the antacid. Thus, a concomitant administration of both substances should be avoided or an administration interval of at least 2 h or more between the drugs should be considered.

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